RECEPTORS AND SIGNALING IN BONE IN HEALTH AND DISEASE

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National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Dental and Craniofacial Research
National Institute on Aging
National Institute of Child Health and Human Development

THIS PA USES THE "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. IT INCLUDES DETAILED MODIFICATIONS TO STANDARD APPLICATION INSTRUCTIONS THAT MUST BE USED WHEN PREPARING APPLICATIONS IN RESPONSE TO THIS PA.

This PA replaces DK-96-076, which was published in the NIH Guide, Vol. 25, No. 33, October 4, 1996.

PURPOSE

The objective of this initiative is to elicit grant submissions that focus on systemic hormones, local growth factors, and bone-active cytokines, their receptors and mechanisms of signaling in bone. While the primary focus is on basic research, the long-term emphasis is on identifying mechanisms or processes related to hormone action with potential applicability as targets for therapeutic agents that may have efficacy in the treatment of diseases that adversely affect bone, such as osteoporosis and primary hyperparathyroidism.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This PA, Receptors and Signaling in Bone in Health and Disease, fits the criteria of Chronic Disabling Diseases. Potential applicants may obtain a copy of "Healthy People 2000" at http://odphp.osophs.dhhs.gov/pubs/hp2000

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign for-profit and nonprofit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal Government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as principal investigators.

MECHANISM OF SUPPORT

This PA will use the National Institutes of Health (NIH) research project grant (R01) award mechanism. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. The total project period for an application submitted in response to this PA may not exceed 5 years.

Specific application instructions have been modified to reflect "MODULAR GRANT" and "JUST-IN-TIME" streamlining efforts being examined by the NIH. Complete and detailed instructions and information on Modular Grants can be found at http://grants.nih.gov/grants/funding/modular/modular.htm

RESEARCH OBJECTIVES

Summary

The NIDDK, NIAMS, NIDCR, and NIA issued a Program Announcement on October 4, 1996 entitled: “Anabolic Hormones in Bone: Basic Research and Therapeutic Potential.” The PA followed the recommendations for research initiatives from a workshop of the same title held May 1-2, 1995, organized by the NIDDK, and co-sponsored by the NIAMS and the NIH Office of Research on Women’s Health. Since that time considerable progress has been made in understanding the roles of hormones, growth factors, and cytokines in the regulation of bone. It is still clear, however, that diseases that affect bone, such as osteoporosis and primary hyperparathyroidism, result in gradual loss of bone and resulting osteopenia (thinning of the bones), a leading cause of fractures in adults. Research has shown that this is particularly prevalent in postmenopausal women, though men are also susceptible to osteoporosis. Hormones are major regulators of bone mass and osteopenia may result from alterations in hormone action, such as loss of normal estrogen production in post-menopausal women, excessive production of parathyroid hormone (PTH) as in primary hyperparathyroidism, or glucocorticoid excess as a consequence of chronic steroid use in immunosuppressive therapy.

Moreover, defects in signaling during development can result in severe dysplasias in bone, such as Jansen's dyschondroplasia, caused by aberrant PTHrP signaling. Indeed, studies on bone morphogenesis have revealed roles for signaling through peptides such as sonic hedgehog, PTHrP, BMP, and hox gene products in bone cell fate determination, cell differentiation, and formation of mature bone. That cell signaling in developing and mature bone cells is key to maintaining proper mineral balances and peak bone mass was revealed through studies funded in response to the original PA and other recent initiatives. Other imbalances in local growth factors and/or bone-active cytokines resulting from a variety of conditions may also contribute to osteopenia. Limited clinical trials have determined that hormone replacement can partially mitigate or reverse the osteopenia associated with menopause, hypogonadism or primary hyperparathyroidism. Use of estrogen/progesterone hormone replacement therapy (HRT) has gained wide acceptance in peri- and post-menopausal women, though not without undesired side effects. The development and use of Selective Estrogen Receptor Modulators (SERMs) has served to partially offset the side effects while giving some degree of protection against postmenopausal bone loss. Still other therapeutic agents have been developed that alter mineral content and/or molecular structure of bone (e.g., bisphosphonates) or that alter hormonal balances (e.g., calcitonin, vitamin D).

While the primary focus is on basic research, the long-term emphasis should be on identifying mechanisms or processes associated with hormonal regulation of bone cell structure/function emphasizing signaling in bone cells and their precursors, with potential applicability as therapeutic agents for the treatment of diseases which adversely affect bone, including osteoporosis and primary hyperparathyroidism.

Research Objectives and Scope

The major areas of interest and potential that have been identified relevant to this program announcement are the following:

o The mechanism(s) of action of sex steroids, including estrogen, selective estrogen receptor modulators (SERMs), partial agonists, and agents with estrogen-like activity in bone; androgens and androgen-like agents which express positive, anabolic effects on bone.

o Other members of the nuclear hormone receptor superfamily, including PPAR, vitamin D, and others and their role(s) in signaling in bone cells and bone cell precursors.

o Parathyroid hormone (PTH) and/or parathyroid hormone-related peptide (PTHrP) and agonists or partial agonists which express PTH- or PTHrP-like anabolic effects in bone and the mechanisms of signaling in developing and mature bone.

o Insulin-like growth factor I (IGF-I), receptors, IGF-I binding proteins, or any other component of the IGF axis which signal in bone.

o Fibroblast growth factor(s) and their role(s) in bone/cartilage development and/or angiogenesis related to bone.

o Members of the Bone Morphogenetic Protein family (e.g., TGFs), and other cytokines (e.g., CSF-1), their receptors, and signaling pathways in bone.

o Novel transcription factors, such as osteoprotegrin, Cfba1, other hox gene products, and their mechanisms of signaling in bone cells and their precursors.

o Prostaglandins with effects on bone cells.

o Interleukins, including those that have positive effects and agents which can oppose putative negative effects on bone.

This is by no means a complete listing of potentially important hormones, growth factors, or cytokines. The general focus should be on developing an understanding of the putative mechanism(s) of action of these agents with the goal of defining what aspect(s) of signaling in bone may be affected and how anabolic or other beneficial therapeutic actions may be achieved and sustained. The NIDDK, NIAMS, and NIA share a mission to provide broad fundamental and clinical research support for a spectrum of chronic and disabling diseases that affect bone, including osteoporosis, and other forms of generalized bone loss. The NIDDK has a special interest in primary hyperparathyroidism and the mechanism of action of calciotropic hormones. The NIDCR has a special interest in research focusing on craniofacial bone. The NIA has a special interest in research that addresses changes in the levels of, and biologic responses to, bone regulatory factors as a consequence of aging.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving

human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and in the NIH Guide For Grants and Contracts, Vol. 23, No. 11, March 18, 1994, available on the web at http://grants.nih.gov/grants/guide/notice-files/not94-100.html

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the “NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects” that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: http://grants.nih.gov/grants/guide/notice-files/not98-024.html

Investigators may also obtain copies of these policies from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

APPLICATION PROCEDURES

Applications are to be submitted on the grant application form PHS 398 (rev. 4/98) and will be accepted at the standard application deadlines as indicated in the application kit. Application kits are available at most institutional offices of sponsored research, or may be obtained from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301-435-0714, email: GrantsInfo@nih.gov.

Any applicant planning to submit an investigator-initiated new (type 1) competing continuation (type 2), competing supplement, or any amended/revised version of the preceding grant application types requesting $500,000 or more in direct costs for any year is advised that he or she must contact program staff of the relevant Institute (listed at the end of this announcement) before submitting the application, i.e., as plans for the study are being developed. Furthermore, the application must obtain agreement from the staff that the Institute will accept the application for consideration for award. Finally, the applicant must identify, in a cover letter sent with the application, the staff member and Institute who agreed to accept assignment of the application.

This policy requires an applicant to obtain agreement for acceptance of both any such application and any such subsequent amendment. Refer to the NIH Guide for Grants and Contracts, March 20, 1998 at http://grants.nih.gov/grants/guide/notice-files/not98-030.html

The modular grant concept establishes specific modules in which direct costs may be requested as well as a maximum level for requested budgets. Only limited budgetary information is required under this approach. The just-in-time concept allows applicants to submit certain information only when there is a possibility for an award. It is anticipated that these changes will reduce the administrative burden for the applicants, reviewers, and Institute staff. The research grant application form PHS 398 (rev. 4/98) is to be used in applying for these grants, with the modifications noted below.

BUDGET INSTRUCTIONS

Modular Grant applications will request direct costs in $25,000 modules, up to a total direct cost request of $250,000 per year. (Applications that request more than $250,000 direct costs in any year must follow the traditional PHS 398 application instructions.) The total direct costs must be requested in accordance with the program guidelines and the modifications made to the standard PHS 398 application instructions described below:

PHS 398

o FACE PAGE: Items 7a and 7b should be completed, indicating Direct Costs (in $25,000 increments up to a maximum of $250,000) and Total Costs [Modular Total Direct plus Facilities and Administrative (F&A) costs] for the initial budget period. Items 8a and 8b should be completed indicating the Direct and Total Costs for the entire proposed period of support.

o DETAILED BUDGET FOR THE INITIAL BUDGET PERIOD: Do not complete Form Page 4 of the PHS 398. It is not required and will not be accepted with the application.

o BUDGET FOR THE ENTIRE PROPOSED PERIOD OF SUPPORT: Do not complete the categorical budget table on Form Page 5 of the PHS 398. It is not required and will not be accepted with the application.

o NARRATIVE BUDGET JUSTIFICATION: Prepare a Modular Grant Budget Narrative page. (See http://grants.nih.gov/grants/funding/modular/modular.htm for sample pages.) At the top of the page, enter the total direct costs requested for each year. This is not a Form page.

o Under Personnel, list key project personnel, including their names, percent of effort, and roles on the project. No individual salary information should be provided. However, the applicant should use the NIH appropriation language salary cap and the NIH policy for graduate student compensation in developing the budget request.

For Consortium/Contractual costs, provide an estimate of total costs (direct plus facilities and administrative) for each year, each rounded to the nearest $1,000. List the individuals/organizations with whom consortium or contractual arrangements have been made, the percent effort of key personnel, and the role on the project. Indicate whether the collaborating institution is foreign or domestic. The total cost for a consortium/contractual arrangement is included in the overall requested modular direct cost amount. Include the Letter of Intent to establish a consortium. Indirect costs for subcontracts are included in the total costs for the application. Provide an additional narrative budget justification for any variation in the number of modules requested.

o BIOGRAPHICAL SKETCH: The Biographical Sketch provides information used by reviewers in the assessment of each individual's qualifications for a specific role in the proposed project, as well as to evaluate the overall qualifications of the research team. A biographical sketch is required for all key personnel, following the instructions below. No more than three pages may be used for each person. A sample biographical sketch may be viewed at: http://grants.nih.gov/grants/funding/modular/modular.htm

- Complete the educational block at the top of the form page;
- List position(s) and any honors;
- Provide information, including overall goals and responsibilities, on research projects ongoing or completed during the last three years.

- List selected peer-reviewed publications, with full citations;

o CHECKLIST: This page should be completed and submitted with the application. If the F&A rate agreement has been established, indicate the type of agreement and the date. All appropriate exclusions must be applied in the calculation of the F&A costs for the initial budget period and all future budget years.

o The applicant should provide the name and phone number of the individual to contact concerning fiscal and administrative issues if additional information is necessary following the initial review. The program announcement title and number must be typed on line 2 of the face page of the application form and the YES box must be marked.

Submit the signed, original, single-sided application, including the Checklist, along with five signed photocopies and five collated sets of appendix materials in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040-MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

The Center for Scientific Review (CSR) will not accept any application in response to this PA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an introduction addressing the previous critique.

REVIEW CONSIDERATIONS

Applications will be assigned on the basis of established Public Health Service referral guidelines. Applications will be evaluated for scientific and technical merit by an appropriate scientific review group convened in accordance with the standard NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed, assigned a priority score, and receive a second-level review by the appropriate national advisory council or board.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewer will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

o Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

o Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

o Innovation: Does the project employ novel concepts, approaches, or method? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

o Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

o Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

o Adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

o The reasonableness of the proposed budget and duration to the proposed research.

o The adequacy of the proposed protection of humans, animals, or the environment, to the extent that they may be adversely affected by the project proposed in the application.

o Availability of special opportunities for furthering research programs through the use of unusual talent resources, populations, or environmental conditions in other countries which are not readily available in the United States or which provide augmentation of existing U.S. resources.

AWARD CRITERIA

Applications will be assigned to Institutes for possible funding according to existing referral guidelines, and will compete for available funds with all other recommended applications assigned to the participating Institutes. The following will be considered in making funding decisions:

o Quality of the proposed project as determined by peer review;
o Availability of funds;
o Program priority.

INQUIRIES

Inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

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Direct inquiries regarding fiscal and administrative matters to:

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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.847 (NIDDK), 93.846 (NIAMS), 93.121 (NIDCR), 93.866 (NIA) and 93.865 (NICHD). Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under NIH grants policies and Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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